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(54) **Pharmaceutical composition and process for preparing the same.**

(57) The invention relates to pharmaceutical compositions as well as the preparation thereof which are useful for improving the status of patients suffering from external otitis or otitis (otitis media), or particularly from a chronic otitis (otitis media chronica) The pharmaceutical compositions according to the invention contain a sulfhydryl-containing compound, an antibacterial chemotherapeutic agent, an aspecific antiinflammatory agent and optionally a keratolytic agent. The compositions preferably contain N-acetyl-L-cysteine as sulfhydryl-containing compound.

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# PHARMACEUTICAL COMPOSITION AND PROCESS FOR PREPARING THE SAME

This invention relates to novel pharmaceutical compositions useful for improving the status of patients suffering from external otitis or otitis (otitis media), particularly from a chronic otitis (otitis media chronica) as well as for restoring the healthy conditions of the middle ear.

According to another aspect of the invention, there is provided a process for the preparation of the novel compositions.

Chronic otitis is a disease occurring in both the adult age and childhood which affects a relatively high percentage of the population. Not only the acute complications but also the bradycusia (hardness of hearing) and surdity emerging later on can be avoided by an early diagnosis and suitable therapy. The deterioration of hearing of about one fourth of all the patients suffering from hardness of hearing can be attributed to inflammations endured in the childhood and developing frequently in connection with infective diseases. Both the subacute and chronic otitis are found in a higher percentage of children who frequently suffered from otitis. Essential characteristics of this disease are a discontinuity of the eardrum, alterations of the tympanic cavity and recurrent recrudescences of the symptoms. In addition to the common reactions following the inflammation, the local symptoms may be manifest or latent. In the absence of a therapy, these processes may lead to life-threatening complications.

In the mesotympanic chronic otitis, the large central eardrum perforation, abundant mucous discharge and mucosa proliferation are characteristic. A bone damage or chronic mastoiditis may easily develop. The microorganisms, which are easy to be cultured from the discharge, belong to Staphylococcus and Pseudomonas genera.

A less and marginal perforation as well as eardrum epithelial metaplasia and a lower extent of discharge are characteristic of the epitympanic chronic otitis: the discharge is very thick, frequently purulent and stinking. The keratinizing flat epithelium of the auditory meatus penetrates into the tympanic cavity, replaces the mucous membrane taking place there under normal conditions and, due to the continuous detachments, forms there an epithelial cell mass, the so-called cholesteatoma. This thick mass spoils the bone formations of the tympanic cavity and finally, it may induce life-threatening complications. The inflammation occurring in such cases is not only a process of the mucous membrane but also extends to the bone. The superinfection is also characteristic of this form of the chronic otitis.

Thus, the characteristic feature of chronic otitis in these cases consists therein that, due to the discontinuity of the eardrum, the tympanic cavity has a free contact with the outside world and, with the advance of the pathologic processes an irreversible damage of the eardrum takes place and thereby, considerable auditory defect is induced which is increasing parallelly with the duration of the disease. In addition, the eardrum may completely be deleted as a consequence of the inflammatory processes.

Earlier ear drops containing boric acid, alcohol, hydrogen peroxide, silver nitrate, trichloroacetic acid, ultraseptyl, balsamics or chloramphenicol were suggested for the therapy of such diseases. These ear drops were useful for the symptomatic treatment and for abolishing the symptoms of the secondary superinfection, however, they were not capable to promote the removal of the discharge or the cholesteatoma and to prevent simultaneously the bacterial and fungal infections. Further on, no commonly available composition is known at present which is suitable to alter the consistency of the ear discharge and thus to promote the easier leaving or the removal of the discharge from the ear. There are frequently described otologic compositions which cannot be used for an open tympanic cavity.

There are generally known combinations preferably containing an aminoglycoside antibiotic together with an aspecific antiinflammatory agent. In spite of a possible synergistic effect, such combinations are not capable to cure the complex ear diseases though, in certain cases they can prevent the further propagation of the bacterial infection and the chronic development of inflammations; however, due to their composition, they are unable to promote also the simultaneous leaving of the discharges in addition to the above-mentioned treatment of the ear discharge. Namely, when investigating the etiology of otitis, this is indispensable.

Based on these knowledges, the aim of the present invention is to provide compositions which exert an adequate mucolytic and/or keratolytic effect in the case of a perforated eardrum and are capable to suppress the destructive effects of bacteria and fungi.

The invention is based on the surprising recognition that, due to their mucolytic and keratolytic effects, compounds containing sulfhydryl group(s) together with other commonly known drugs can successfully be used for curing patients suffering from chronic otitis (otitis media chronica).

The mucolytic action of a group of sulfhydryl-containing compounds for curing respiratory diseases has been described in several forms. A number of pharmaceutical compositions containing such active

ingredients such as Mucomyst, Mucolyticum Lappe, Fluimucil, Aibron, Acetein and Mucosolvin are commercially available.

The utility of sulfhydryl-containing compounds for reducing the mucous viscosity was proved in a number of cases both by local and oral or parenteral treatments as well. One of the most commonly used  
5 sulfhydryl-containing compounds is acetylcysteine satisfying the requirements of an oral administration on the basis of its LD<sub>50</sub> values:

LD<sub>50</sub> in dogs = 1000 mg/kg of body-weight;

LD<sub>50</sub> in rats = 6000 mg/kg of body-weight; and

LD<sub>50</sub> in mice = 3000 mg/kg of body-weight.

10 In the respiratory diseases the implantation of bacterial flora becomes more difficult simultaneously with the decrease of the mucous viscosity. According to an other important observation, the bacteria are neither encapsulated nor morphologically altered in the presence of sulfhydryl-containing compounds.

This observation can be explained by the mode of action of the sulfhydryl-containing compounds, more particularly by the exchange reactions resulting in the separation of peptide chains.

15 The invention is based on the observation that, similarly to the respiratory diseases, a highly viscous superinfected discharge of a high protein content is formed in most patients suffering from otitis (otitis media) which discharge is frequently unable to flow out even through the perforated eardrum. During our investigations, it has surprisingly been found that, in a suitable environment, compounds containing sulfhydryl group(s) are capable in vitro to reduce the viscosity of these types of discharges rapidly and  
20 significantly. In the presence of sulfhydryl-containing compounds, e.g. several acylcysteines at a pH value of 6.7 to 7.5, the ear discharges taken from the patients become in vitro liquid within a short time.

In our further investigations involving cases with inflammation and superinfection, sulfhydryl compounds of different structure were combined with antibacterial, aspecific antiinflammatory and optionally keratolytic drugs. In accord with the observation of the prior art, it has been found that, in the cases of several  
25 combinations, the compounds containing reactive sulfhydryl groups are capable to take part in an undesired reaction with some aldehydes, epoxides lactones and  $\beta$ -lactams [Eur. J. Respir. Dis. 61, Suppl. II, pp. 151-157 (1980)]. However, the absorption of several antibiotics from the stomach is not disadvantageously influenced by the sulfhydryl-containing compounds, particularly by acetylcysteine. Such antibiotics include inter alia amoxicillin, tobramycin, doxycyclin, neomycin and erythromycin. A certain but not significant  
30 extent of retardation may be observed with cephalixin; however, by assuring a relatively acidic pH value, this extent can be reduced. Based on these findings, it seemed possible to provide conditions, where the sulfhydryl-containing compounds are present in a stable composition together with the antibiotic types mentioned above.

According to the observation of M. F. Parry et al. [J. Clin. Microbiol. 5, pp. 58-61 (1977)], compounds  
35 containing a sulfhydryl group, particularly the acylcysteines are capable to inhibit the growth of several gram-positive and gram-negative bacteria such as *Pseudomonas aeruginosa*. Under the experimental conditions used, acetylcysteine shows a synergistic effect with several antibiotics under in vitro conditions.

Further on, our investigations led to the result that, out of the compounds containing a sulfhydryl group, N-acetyl-L-cysteines and their pharmaceutically acceptable salts such as the sodium or ammonium salt or  
40 the zinc mercaptide salt give the best results; however, a mucolytic effect can also be shown by using other compounds such as dithioerythritol, disulfiram, dimercaptosuccinate, glutathione, pantetheine or carbocysteine.

Within our investigations, acetylcysteine, particularly N-acetyl-L-cysteine proved to be the most useful mucolytic agent showing a pH value between 2.0 and 2.76 in an aqueous solution of 1 % concentration.

45 The N-acetyl-L-cysteine shows the highest viscosity-reducing action at a pH between 6.0 and 8.0. When this agent is used in the form of its pharmaceutically acceptable salts, the pH-dependance is not so much significant, however, the mucolytic activity of the salts is lower than that of the N-acetyl-L-cysteine [Am. Rev. Respir. Dis. 90, pp. 721-729 (1964)].

For combatting the bacterial infection occurring in the inflammation antibacterial chemotherapeutics,  
50 commonly employed in the dermatological therapy may be used. Such drugs are e.g. neomycin, polymyxin B, gentamycin, tobramycin, paromomycin, tetracyclins, chloramphenicol, nitrofurazone derivatives, tyrothricine, fusidic acid, amphomycin, the penicillins and cephalosporins as well as the therapeutically acceptable derivatives of these compounds.

In the compositions according to the invention steroids, synthetic corticoids such as hydrocortisone,  
55 dexamethasone, fluocinolone, fludroxycorticoid, cortisone acetate, triamcinolone acetonide, fluocinolone acetonide, mazipredone hydrochloride and beclomethasone dipropionate are preferably used as antiinflammatory agents.

The compositions according to the invention may optionally contain also desquamatory agents such as

tretinoin, salicylic acid or its derivatives as well as benzoic acid and resorcinol. The compounds investigated are usually capable to remove effectively the flat epithelium penetrating into the tympanic cavity or the cholesteatoma.

5 The most preferred formulation of the mucolytic and chemotherapeutic compositions according to the invention is the ear drop namely, the drops, having a liquid consistency penetrate easily to the sites of the accumulated thick and viscous discharge and promote its relatively easy removal.

In the course of therapeutically investigating the ear drops of the above composition, the following observations have been made.

10 In the case of external diffuse eczematous otitis (otitis externa diffusa ekzematosa) the effect was very favourable: an improvement or restoration was observed in about 86% of the patients. Furthermore, a great part of the improved cases could be completely cured by a drying post-treatment.

In the cases of chronic cholesteatomatous otitis (otitis media chronica cholesteatomatosa), it could be observed that the cholesteatomatous mass was more easily removable by an otologic aspirating equipment than in the cases without the treatment.

15 During the therapeutical study of the composition according to the invention, the advance of the pathological process was not observed in any case; no side-effect appeared which could motivate to cease the treatment.

By using the compositions according to the invention, the period of the restoration was reduced thus, the pathological state was much earlier improved. It is thought to be most important that after the use of the composition according to the invention the amount of the ear discharge was suddenly reduced and its consistency was also significantly modified. The ear discharge did not become in general more thin-liquid but its viscosity was diminished by obtaining a precipitate-like character. No increase in the amount of discharge was observed.

20 Several compositions according to the invention were also studied with omitting one active ingredient of the composition in order to support the progressive character of the multi-active-component type composition according to the invention. These experiments led to the following results.

The use of an 1% tobramycin solution resulted in a substantial improvement of the pathological processes in about 60% of patients suffering from chronic mesotympanic otitis; this ratio did not exceed the 40% in the patients suffering from external otitis.

30 When administering only a steroid, the greater part of the patients were subjectively improved however, the objective signs of the improvement were not convincing. An objective improvement was observed only in those cases involving large eardrum defects, strong hyperaemia and significant mucous membrane hypertrophy of the tympanic cavity as well as in the cases of external eczematous otitis (otitis externa ekzematosa).

35 Surprisingly, aqueous solutions (pH  $7.0 \pm 0.2$ ) of 3 to 19%, preferably 5 to 15% of compounds containing the sulfhydryl group such as acylcysteines, preferably N-acetyl-L-cysteine advantageously influenced the viscosity of the discharge and simultaneously moderated the inflammatory symptoms, too. The dilution of the discharge was not observed during the use, however, the amount of the discharge was somewhat reduced in spite of the decrease of its viscosity. The discharge, which was coherent and mucous in character, rather took the form of a precipitate under effect of the treatment by an acetylcysteine solution.

40 In the Department for Otorhinolaryngology of the Medical University of Debrecen, adult and child patients were examined to identify the types of pathogenic microorganisms occurring in the discharges of patients suffering from chronic otitis (otitis media chronica); the discharges of 510 patients were analyzed for the bacterial infection. The results obtained by the analysis of the ear discharge of 279 children and 231 adults are summarized in Table 1.

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Table 1

The frequency of pathogenic microorganisms		
Pathogen	Number of cases	% of cases
Staphylococcus aureus	164	32.15
Pseudomonas aeruginosa	78	15.29
Staphylococcus epidermidis	71	13.92
Pseudomonas sp.	39	7.64
Proteus sp.	32	6.27
Escherichia coli	31	6.07
Klebsiella sp.	23	4.5
Streptococcus alpha-haemolyticus	14	2.74
Bacillus sp.	13	2.54
Streptococcus faecalis	11	2.15
Streptococcus beta-haemolyticus	10	1.96
Escherichia alkal. dispar	8	1.56
Streptococcus pneumoniae	7	1.37
Haemophilus sp.	5	0.98
Acinetobacter sp.	3	0.58
Alcaligenes faecalis	1	0.19
	510	100.00

It was concluded from the observations that an important identity of the bacterial infection exists in the otitis cases of adult and child patients. As it can clearly be seen from Table 1, the most frequently occurring pathogens are Staphylococcus aureus, Pseudomonas aeruginosa and Staphylococcus epidermidis.

Hereinafter, the results of the treatment of the discharges by antibacterial agents are summarized in Table 2.

Table 2

Active ingredient	Ø	R	M	A	Act.
Neomycin	465	5	13	27	88.9
Tobramycin	247	61	86	116	79.2
Oxacillin	229	77	13	191	72.6
Meticillin	242	95	27	146	64.6
Carbenicillin	260	91	22	137	63.6
Gentamycin	255	118	72	65	53.7
Cephalexin	131	182	27	170	51.9
Streptomycin	342	87	42	39	48.2
Polymyxin B	330	103	8	69	42.7
Ampicillin	307	120	11	72	40.8
Oleandomycin	213	179	4	114	39.7
Chloramphenicol	196	197	11	106	37.2
Co-trimoxazole	99	259	12	140	36.9
Erythromycin	183	208	6	113	36.4
Penicillin	203	218	22	67	29.4
Tetracyclin	136	279	16	79	25.4
Total number of the examinations: 510					
Symbols used in Table 2:					
Ø = number of the cases not examined					
R = inactive (resistant)					
M = moderately active					
A = therapeutically active (sensitive)					
Act. = activity %					

In the course of investigation of the fungi species occurring in the ear discharges it was determined that, in accord to the literature, the most characteristic species in this disease are *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger* and *Candida albicans*.

The ear drop compositions according to the invention are prepared as described hereinafter.

About one half of the required amount of propylene glycol is added to the most part of the required amount of water then, with keeping of the following order of addition, the sulfhydryl-containing compound is first added, which compound is preferably completely soluble in the medium or suitable to form a microcrystalline suspension. After an eventual clearing of the solution zinc oxide is added which may be dissolved even in one hour even while stirring. Zinc oxide is used for stabilizing the sulfhydryl compounds.

Subsequently, the pH value of the solution or suspension is modified by adding preferably sodium hydroxide, then the antibacterial ingredient suitably chosen from the group of the aminoglycosides is introduced. After adding the second half of propylene glycol, the antiinflammatory ingredient is added, while taking care to maintain the pH value at  $7.0 \pm 0.1$  by portionwise addition of 1M sodium hydroxide solution. On introducing the anti inflammatory agent the complete dissolution is not required in each case; optionally a microcrystalline suspension is prepared.

After introducing the antiinflammatory ingredient the other auxiliary and additive materials are added, then if necessary the solution is filtered and formulated in each case in a sterile form.

The compositions and process according to the invention are illustrated in detail in the following non-limiting Examples.

Example 1	
Preparation of a microcrystalline suspension	
Components:	
N-Acetyl-L-cysteine	500 mg
Tobramycin sulfate	100 mg
Hydrocortisone acetate (microcrystalline)	100 mg
Neomycin sulfate	100 mg
Aqueous solution of propylene glycol up to	10.0 ml

Example 2	
Preparation of a solution	
Components:	
N-Acetyl-L-cysteine	500 mg
Tobramycin sulfate	100 mg
Mazipredone hydrochloride	50 mg
Neomycin sulfate	100 mg
Aqueous solution of propylene glycol up to	10.0 ml

Example 3	
Components:	
N-Acetyl-L-cysteine	500 mg
Polymyxin B sulfate	100,000 IU
Neomycin sulfate	100 mg
Mazipredone hydrochloride	50 mg
Aqueous solution of propylene glycol up to	10.0 ml

Example 4	
Components:	
Disulfiram	500 mg
Salicylic acid	500 mg
Polymyxin B sulfate	100,000 IU
Neomycin sulfate	100 mg
Hydrocortisone acetate	100 mg
Aqueous solution of propylene glycol up to	10.0 ml

Example 5	
Components:	
Pantetheine	450 mg
Benzoic acid	100 mg
Polymyxin B sulfate	100,000 IU
Neomycin sulfate	100 mg
Beclomethasone dipropionate	100 mg
Aqueous solution of propylene glycol up to	10.0 ml

Example 6	
Components:	
N-Acetyl-L-cysteine	850 mg
Tobramycine sulfate	100 mg
Hydrocortisone acetate (microcrystalline)	100 mg
Aqueous solution of propylene glycol up to	10.0 ml

Example 7	
Components:	
N-Acetyl-L-cysteine	1100 mg
Neomycin sulfate	100 mg
Mazipredone hydrochloride	60 mg
Aqueous solution of propylene glycol up to	10.0 ml

Example 8	
Components:	
N-Acetyl-L-cysteine	600 mg
Tobramycin sulfate	100 mg
Triamcinolone acetonide	40 mg
Benzoic acid	120 mg
Aqueous solution of propylene glycol up to	10.0 ml

Example 9	
Components:	
N-Acetyl-L-cysteine	500 mg
Tobramycin sulfate	125 mg
Hydrocortisone acetate (microcrystalline)	100 mg
Aqueous solution of propylene glycol up to	10.0 ml



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Example 10	
Components:	
N-Acetyl-L-cysteine	600 mg
Tobramycin sulfate	125 mg
Mazipredone hydrochloride	50 mg
Aqueous solution of propylene glycol up to	10.0 ml

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Example 11	
Components:	
N-Acetyl-L-cysteine	550 mg
Tobramycin sulfate	125 mg
Dexamethasone sodium phosphate	10 mg
Aqueous solution of propylene glycol up to	10.0 ml

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Example 12	
Components:	
N-Acetyl-L-cysteine	700 mg
Polymyxin B sulfate	100,000 IU
Tobramycin sulfate	125 mg
Prednisolone sodium succinate	50 mg
Aqueous solution of propylene glycol up to	10.0 ml

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Example 13	
Components:	
Disulfiram	500 mg
Salicylic acid	500 mg
Polymyxin B sulfate	100,000 IU
Gentamycin sulfate	100 mg
Dexamethasone sodium phosphate	10 mg
Aqueous solution of propylene glycol up to	10.0 ml

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Example 14	
Components:	
Pantetheine	450 mg
Benzoic acid	100 mg
Polymyxin B sulfate	100,000 IU
Tobramycin sulfate	100 mg
Betamethasone disodium phosphate	10 mg
Aqueous solution of propylene glycol up to	10.0 ml

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## Claims

1. An ear drop composition comprising:  
a compound containing sulfhydryl group(s),  
an antibacterial agent,  
an antiinflammatory agent, and  
an otologically acceptable carrier.
2. A composition according to claim 1 wherein the sulfhydryl group containing compound is an acylcysteine, dithioerythritol, pantetheine, disulfiram or dimercaptosuccinate.
3. A composition according to claim 2 wherein the acylcysteine is N-acetyl-L-cysteine or a pharmaceutically acceptable salt thereof.
4. A composition according to claim 3 wherein the N-acetyl-L-cysteine is in the form of a sodium, ammonium or zinc mercaptide salt.
5. A composition according to any preceding claim further comprising neomycin, polymyxin B, gentamycin, tobramycin, paromomycin, tetracyclin, chloramphenicol, a nitrofurazone derivative, tyrothricine, fusidic acid, amphotomycin, penicillin or a cephalosporin derivative as an antibacterial chemotherapeutic agent.
6. A composition according to any preceding claim wherein the antiinflammatory agent is a synthetic corticoid, hydrocortisone, hydrocortisone acetate, dexamethasone, fluocinolone, fludroxycorticoid, cortisone acetate, triamcinolone acetonide, mazipredone hydrochloride or beclomethasone dipropionate.
7. A composition according to any preceding claim further comprising a keratolytic agent.
8. A composition according to claim 7 wherein the keratolytic agent is salicylic acid or a derivative thereof, benzoic acid, tretinoin or resorcinol.
9. A composition according to claim 7 or claim 8 which comprises 1 to 11% by mass of the keratolytic agent.
10. A composition according to any preceding claim which comprises 3 to 19% by mass of the compound containing sulfhydryl group(s), 0.01 to 6.0% by mass of the antibacterial agent, and 0.01 to 5.0% by mass of the antiinflammatory agent.
11. A composition according to claim 10 which comprises 5 to 15% by mass of the compound containing sulfhydryl group(s) and 0.1 to 3.0% by mass of an antibacterial agent.
12. The use of  
a compound containing sulfhydryl group(s),  
an antibacterial agent, and  
an antiinflammatory agent  
for the manufacture of an ear drop composition for the treatment of otitis.

Claims for the following Contracting States: ES,GR

1. The use of a compound containing sulfhydryl group(s),  
an antibacterial agent, and  
an antiinflammatory agent  
for the manufacture of an ear drop composition for the treatment of otitis.
2. The use according to claim 1 further comprising an otologically acceptable carrier as an ingredient of the ear drop composition.
3. The use according to claim 1 or claim 2 wherein the sulfhydryl group containing compound is an acylcysteine, dithioerythritol, pantetheine, disulfiram or dimercaptosuccinate.
4. The use according to claim 3 wherein the acylcysteine is N-acetyl-L-cysteine or a pharmaceutically acceptable salt thereof.
5. The use according to claim 4 wherein the N-acetyl-L-cysteine is in the form of a sodium, ammonium or zinc mercaptide salt.
6. The use according to any preceding claim further comprising neomycin, polymyxin B, gentamycin, tobramycin, paromomycin, tetracyclin, chloramphenicol, a nitrofurazone derivative, tyrothricine, fusidic acid, amphotomycin, penicillin or a cephalosporin derivative as an antibacterial chemotherapeutic agent in the ear drop composition.
7. The use according to any preceding claim wherein the antiinflammatory agent is a synthetic corticoid, hydrocortisone, hydrocortisone acetate, dexamethasone, fluocinolone, fludroxycorticoid, cortisone acetate, triamcinolone acetonide, mazipredone hydrochloride or beclomethasone dipropionate.

8. The use according to any preceding claim further comprising a keratolytic agent as an ingredient of the ear drop composition.

9. The use according to claim 8 wherein the keratolytic agent is salicylic acid or a derivative thereof, benzoic acid, tretinoin or resorcinol.

- 5 10. A method for preparing an ear drop composition comprising the step of mixing together:  
a compound containing sulfhydryl group(s),  
an antibacterial agent,  
an antiinflammatory agent, and  
an otologically acceptable carrier.

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	US-A-3 091 569 (A.L. SHEFFNER) * Column 3, lines 40-50; column 6, lines 27-34 * ---	1-12	A 61 K 31/71 // (A 61 K 31/71 A 61 K 31:60 A 61 K 31:57 A 61 K 31:195)
X	FR-M- 2 470 (MEAD JOHNSON & CO.) * Page 2, right-hand column; page 4, right-hand column * ---	1-12	
Y	ROTE LISTE, 1979, pages 177-178, no. 23 177B, Editio Cantor, Aulendorf, DE; "Fluimucil Antibiotic" * The whole abstract * ---	1-12	
Y	FR-M- 5 691 (MEAD JOHNSON & CO.) * Page 6, abstract * -----	1-12	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 25-01-1989	Examiner BRINKMANN C.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document			